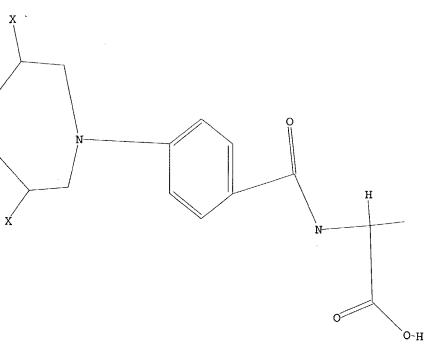
> d 11 1 HAS NO ANSWERS 1 STR



tructure attributes must be viewed using STN Express query preparation.

> s l1 full

## REG1stRY INITIATED

ubstance data SEARCH and crossover from CAS REGISTRY in progress... se DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

ULL SEARCH INITIATED 10:16:53 FILE 'REGISTRY' ULL SCREEN SEARCH COMPLETED - 41 TO ITERATE

00.0% PROCESSED 41 ITERATIONS

EARCH TIME: 00.00.01

1 SEA SSS FUL L1

3 1 L2

2

> d ibib abs hitstr

ANSWER 1 OF 1 CAPLUS COPYRIGHT 2004 ACS on STN

CCESSION NUMBER: 2000:707131 CAPLUS

OCUMENT NUMBER: 133:267154

ITLE: Preparation of nitrogen mustard compounds and prodrugs NVENTOR(S):

Springer, Caroline Joy; Davies, Lawrence Christopher

1 ANSWERS

ATENT ASSIGNEE(S): Cancer Research Campaign Technology Limited, UK OURCE:

PCT Int. Appl., 73 pp.

CODEN: PIXXD2

OCUMENT TYPE: Patent ANGUAGE: English

AMILY ACC. NUM. COUNT:

ATENT INFORMATION:

-							DATE		APPLICATION NO.					DATE			
WO 2000058271																	
																CN,	
		•	•		•	•			-	-						HR,	-
		ID,	IL,	IN,	ıs,	JP,	KE,	KG,	KP,	KR,	KZ,	LC,	LK,	LR,	LS	LT,	LU,
		LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	NO,	NZ,	PL,	PT,	RO,	RU,	SD,	SE,
		SG,	SI,	SK,	SL,	TJ,	TM,	TR,	TT,	TZ,	UA,	UG,	US,	UZ,	VN,	YU,	ZA,
											TM						
	RW:	GH,	GM,	KE,	LS,	MW,	SD,	SL,	SZ,	TZ,	ŪĠ,	ZW,	AT,	BE,	CH,	CY,	DE,
		DK,	ES,	FI,	FR,	GB,	GR,	ΙE,	IT,	LU,	MC,	NL,	PT,	SE,	BF,	ВJ,	CF,
		CG,	CI,	CM,	GΑ,	GN,	GW,	ML,	MR,	ΝE,	SN,	TD,	TG				
AU	AU 2000039746				A5 20001016				AU 2000-39746					20000329			
NZ	IZ 513759				A 20010928				NZ 2000-513759					20000329			
ΕP	1165	1165493				A1 20020102				EP 2000-918981					20000329		
	R:	ΑT,	BE,	CH,	DE,	DK,	ES,	FR,	GB,	GR,	ΙT,	LI,	LU,	ΝL,	SE	MC,	PT,
		ΙE,	SI,	LT,	LV,	FI,	RO										
JP 2002540186				T2 20021126				JP 2000-607975					20000329				
ORITY APPLN. INFO.:									GB 1999-7414						A :	9990	331
									1	WO 2	000-	GB11	94	1	W 2	20000	329
ם מו	OTTO OT	101 .			MADDAM 122.267154												

ER SOURCE(S): MARPAT 133:267154

Ι

Nitrogen mustard compds. and prodrugs I [R = OH or NHCH(Z)CO2R7, resp., where R1, R2 = Cl, Br, I, OSO2Me, or OSO2Ph; R1a, R2a, R1b, R2b = H, Cl-4-alkyl or -haloalkyl; R3 = F, Cl, Br, I, OCHF2, C.tplbond.CH, OCF3, Me, CF3, SF5, SCF3, or CF2CF3; R4 = H, any group given for R3; R5 = H, F; R7 = H, Me3C, allyl; Z = (un)substituted -CH2-T-W, where T = CH2, O, S, S(O), or SO2; W = CO2H, CONH2, SO2NH2, SO3H, PO3H2, tetrazol-5-yl, heterocyclylthio, etc. (with provisos)] were prepared for use in therapy and treatment, for example, of cancer. Thus, [3,5-difluoro-4-[bis(2-iodoethyl)amino]benzoyl]-L-glutamic acid, prepared via amidation of 3,5-difluoro-4-[bis(2-iodoethyl)amino]benzoic acid with di-tert-butyl-L-glutamate hydrochloride, showed antitumor activity against breast carcinoma in mice at 0.98 mM vs. 2.9 mM for the prior art compound [3-fluoro-4-[bis(2-chloroethyl)amino]benzoyl]-L-glutamic acid. 298211-06-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

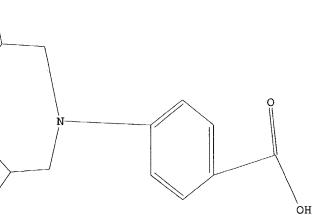
olute stereochemistry.

RENCE COUNT:

THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

## STRUCTURE UPLOADED

Ы HAS NO ANSWERS STR



ructure attributes must be viewed using STN Express query preparation.

## s 14 full

## REG1stRY INITIATED

ostance data SEARCH and crossover from CAS REGISTRY in progress... e DISPLAY HITSTR (or FHITSTR) to directly view retrieved structures.

LL SEARCH INITIATED 10:18:38 FILE 'REGISTRY' LL SCREEN SEARCH COMPLETED - 713 TO ITERATE

0.0% PROCESSED 713 ITERATIONS 2 ANSWERS

ARCH TIME: 00.00.01

2 SEA SSS FUL L4

7 L5

s 16 and py<1999 18920347 PY<1999

6 L6 AND PY<1999

d 1-6 ibib abs hitstr

ANSWER 1 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

CESSION NUMBER:

1979:167816 CAPLUS

CUMENT NUMBER:

90:167816

TLE:

Some physicochemical properties and reactivity of

p-[bis(2-chloroalkyl)amino]phenylalkanoic acids Karpavicius, K.; Juodvirsis, A.; Prasmickiene, G.;

Knunyants, I. L.

RPORATE SOURCE:

Inst. Elementoorg. Soedin., Moscow, USSR

JRCE:

THOR(S):

Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya (

**1979**), (1), 51-8

CODEN: IASKA6; ISSN: 0002-3353

CUMENT TYPE:

Journal

NGUAGE: Russian

In p-(ClCHRCH2)2NC6H4(CH2)nCO2H (I; R = H, Me; n = 0-3) the cytotoxic

amino groups exhibit an appreciable electron-donating effect, whereas the
carboxyalkyl groups show a weaker effect. The CH2 protons in the amino
group of I (R = H; n = 1-3) are magnetically equivalent; those in I (R = H; n
= 0) and the analogous cinnamic acid derivs. are not. The hydrolysis of
C-Cl in I appears to be 1st order; that of I (R = Me) is an order of
magnitude faster than that of I (R = H).
5379-46-4
RL: PRP (Properties)
 (NMR of)
5379-46-4 CAPLUS

Benzoic acid, 4-[bis(2-chloropropyl)amino]- (9CI) (CA INDEX NAME)

ANSWER 2 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

CCESSION NUMBER:

1978:58444 CAPLUS

OCUMENT NUMBER:

88:58444

COMENI NOMBER:

Physicochemical properties and antileukemia activity

ITLE:

of some p-[bis(2-chloropropyl)amino] - and

p-[bis(2-chloroethyl)amino]phenylalkanoic acid

derivatives

JTHOR(S):

Karpavicius, K.; Prasmickiene, G.; Juodvirsis, A.;

Ivanova, L. E.; Khomchenovskii, E. I.

ORPORATE SOURCE:

Inst. Biokhim., Vilnius, USSR

OURCE:

Poiski Izuch. Protivoopukholevykh,

Protivovospalitel'nykh Mutagennykh Veshchestv (

1977), 66-75. Editor(s): Kanopkaite, S.

Akad. Nauk Lit. SSR, Inst. Biokhim.: Vilnius, USSR.

CODEN: 37BOA3

OCUMENT TYPE:

Conference

ANGUAGE:

Russian

Ι

The rate of hydrolysis, pKa, PMR spectra, LD50, and antileukemic effects of 8 p-[bis(2-chloroalkyl)amino]phenylalknoic acids (I) were presented. The 2-chloropropyl derivs. had a greater reactive capacity than did the 2-chloroethyl derivs. owing to the presence of the electron-donor Me group. The 2-chloropropyl derivs. were also generally more toxic than the 2-chloroethyl groups. The 2-chloropropyl derivs. were effective against granulocytopoiesis and on transplanted leukemias Nk/Ly and L-1210 in mice, whereas the 2-chloroethyl derivs. were effective against lymphopoiesis and development of Shchvetz leukemia in rats.

5379-46-4

RL: BIOL (Biological study)

(antileukemic activity and physicochem. properties of)

5379-46-4 CAPLUS

Benzoic acid, 4-[bis(2-chloropropyl)amino]- (9CI) (CA INDEX NAME)

$$C1$$
 $CH_2-CH-Me$ 
 $CH_2-CH-Me$ 
 $CO_2H$ 

ANSWER 3 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

CESSION NUMBER:

1978:15944 CAPLUS

CUMENT NUMBER:

88:15944

TLE:

Comparative study of the general toxicity and antileukemic activity of new phenylalkanoic acid derivatives under experimental conditions

Ivanova, L. E.; Zaretskii, I. I.; Khomchenovskii, E.

I.; Karpavicius, K.; Prasmickiens, G.

RPORATE SOURCE:

Moscow, USSR

THOR(S):

JRCE:

Leikozologiya (1975), 4, 23-9

CODEN: LEIKDK

CUMENT TYPE:

Journal Russian

**NGUAGE:** 

$$1 \text{CH}_2 \text{CH}_2 \text{)}_{\text{mN}} - \text{(CH}_2 \text{)}_{\text{n}} \text{CO}_2 \text{H}$$

The toxicity and antileukemic effects of 8 phenylalkanoic acids (I) were determined The 2-chloropropyl derivs., p-di(2-chloropropyl)aminobenzoic acid [5379-46-4], p-di(2-dichloropropyl)aminophenylacetic acid [19521-09-6], p-di-(2-chloropropyl)aminophenylpropionic acid [22812-54-0], and p-di(2-chloropropyl) aminophenylbutyric acid [55774-31-7] had greater antileukemic effects than the resp. 2-chloroethyl derivs. although LD50 values tended to be lower. 5379-46-4 RL: BIOL (Biological study) (leukemia inhibition by) 5379-46-4 CAPLUS

Benzoic acid, 4-[bis(2-chloropropyl)amino]- (9CI) (CA INDEX NAME)

$$\begin{array}{c|c} & \text{Cl} \\ \mid & \mid \\ \text{Cl} & \text{CH}_2\text{-CH-Me} \\ \mid & \mid & \mid \\ \text{-CH-CH}_2\text{-N} & \\ \hline & \text{CO}_2\text{H} \end{array}$$

ANSWER 4 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

ESSION NUMBER:

1969:430178 CAPLUS

UMENT NUMBER:

71:30178

LE:

HOR (S):

Synthesis and study of the reactivity of

p-[bis(2-chloropropyl)amino]phenylalkanoic acids Prasmickiene, G.; Sukeliene, D.; Karpavicius, K.;

Kil'disheva, O. V.

RPORATE SOURCE: Nauch.-Issled. Inst. Onkol., Vilnius, USSR JRCE: Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya ( 1969), (3), 643-6 CODEN: IASKA6; ISSN: 0002-3353 CUMENT TYPE: Journal IGUAGE: Russian To 2.2 ml. POCl3 in Me2NCHO was added 5.72 q. p-(ClCHMeCH2)2NC6H4NH2 in the same solvent and the mixture kept 1 day at 40° to give p-(ClCH-MeCH2)2NC6H4CHO, (I), m.  $104-6^{\circ}$ . I with N2H4 gave the appropriate ylidenehyrazine, m.  $167-9^{\circ}$ , while HONH2 gave the oxime, m. 125-7°, which after 3 hrs. reflux in Ac20 gave 71% p-(ClCHMeCH2)2NC6H4CN, m. 128-30°, which heated in concentrated H2SO4 2 hrs. at 50° gave the corresponding amide, m. 138-40°. Oxidation of the aldehyde or heating the benzamide with HCl gave p-(ClCHMeCH2)2NC6H4CO2H, m. 160-2°. Propylene oxide added to p-H2NC6H4CH2CH2CONH2 in 30% AcOH gave, in 1 day, 77% (HOCHMeCH2) 2NC6H4CH2CH2CONH2, m. 102-4°, which, heated with POCl3 1 hr., gave, on quenching in ice, 73% p-(C1CHMeCH2)2NC6H4CH2CH2CN (II), m. 66-8°, which in concentrated H2SO4 2 hrs. at 50° gave the corresponding amide, m. 58-60°. I heated with malonic acid in pyridine-piperidine 3 hrs. gave 76% p-(ClCHMeCH2)2NC6H4CH:CHCO2H (III), m. 131-3°. II heated with concentrated HCl gave 59% corresponding free acid, m. 69-71°, also formed by hydrogenation of III over PdCaCO3. 5379-46-4P RL: SPN (Synthetic preparation); PREP (Preparation) (preparation of) 5379-46-4 CAPLUS Benzoic acid, 4-[bis(2-chloropropyl)amino]- (9CI) (CA INDEX NAME) C1 $\mathrm{CH_2}-\mathrm{CH}-\mathrm{Me}$ - CH— CH2— N. CO<sub>2</sub>H

CESSION NUMBER: 1966:84288 CAPLUS CUMENT NUMBER: 64:84288 IGINAL REFERENCE NO.: 64:15785d-g Tumor chemotherapy. XXX. Studies on the CLE: hexamethylenetetramine salt of p-bis(2- $\texttt{chloroethyl)} \, \, \texttt{amino-} \omega \text{-} \texttt{bromoacetophenone} \,$ THOR (S): Jen, Yun-Feng; Kao, I-Sheng RPORATE SOURCE: Inst. Mater. Med., Acad. Sinica, Shanghai, Peop. Rep. China JRCE: Huaxue Xuebao (1965), 31(6), 486-92,500 CODEN: HHHPA4; ISSN: 0567-7351 CUMENT TYPE: Journal IGUAGE: Chinese cf. CA 63, 17000b. p-(XRCHCH2)2NC6H4COCH2[(CH2)6N4]+Br- (Ia) (X = Br, R =  $(1 - 1)^{-1}$ H) (I), (X = I, R = H) (II), p-EtO2CNHC6H4COCH2[(CH2)6N4]+Br- (III), and p-EtO2CNHC6H4COCH2SC(:NH2+Br-)NH2 (IV), the analogs of the antitumor compound AT-584, were prepared The starting materials for the synthesis of I

and II were p-bis[2-haloethyl (and propyl)] aminobenzoic acids (V and VI), resp. VI was synthesized by 2 methods: (1) [R(HO)CHCH2]2NC6H4CO2Et-p was

first halogenated with PBr3 or POCl3 and then hydrolyzed with HCl or HBr to yield p-bis[2-chloropropyl (and 2-bromoethyl)] aminobenzoic acids. (2 Chlorination of p-bis(2-hydroxypropyl)aminobenzene with POCl3 in

dimethylformamide gave p-bis(2-chloropropyl)aminobenzaldehyde, which was treated with KMnO4 in acetone to afford VI. The 2nd route gave a better yield. V and VI in benzene reacted sep. with SOC12 to give the acid chlorides, which were treated sep. with diazomethane to yield the

ANSWER 5 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

diazoacetophenones (VII). VII were decomposed in dioxane with HBr to form bromoacetophenone derivs., which treated with hexamethylenetetramine in chloroform gave I and II, resp. p-Aminoacetophenone was treated with ethyl chloroformate in the presence of triethylamine as the condensing agent to form p-ethoxycarbonyliminoacetophenone (VIII). When N, N-diethylaniline was used as the condensing agent instead of triethylamine, the yield was better. VIII was first brominated in acetic acid with Br and then treated with hexamethylenetetramine or thiourea to afford III and IV, resp. Preliminary pharmacol. examns. showed that I and II were as active as AT-584 against HeLa cells in culture medium, while III and IV were less active. 5379-46-4, Benzoic acid, p-[bis(2-chloropropyl)amino]-

(preparation of) 5379-46-4 CAPLUS Benzoic acid, 4-[bis(2-chloropropyl)amino]- (9CI) (CA INDEX NAME)

Cl  $\mathrm{CH_2}-\mathrm{CH}-\mathrm{Me}$ - cн— сн<sub>2</sub>— и

ANSWER 6 OF 6 CAPLUS COPYRIGHT 2004 ACS on STN

CESSION NUMBER: 1951:863 CAPLUS

CUMENT NUMBER: 45:863

IGINAL REFERENCE NO.: 45:139h-i,140a-g

TLE: Aryl-2-haloalkylamines. VII. Some derivatives of

2-naphthyldi(2-haloalkylamines)

THOR (S): Davis, W.; Everett, J. L.; Ross, W. C. J. RPORATE SOURCE:

Roy. Cancer Hosp., London

URCE: Journal of the Chemical Society, Abstracts (

**1950**) 1331-7

CODEN: JCSAAZ; ISSN: 0590-9791

CUMENT TYPE: Journal NGUAGE: Unavailable

cf. C.A. 44, 6838i. This work is a continuation of that in C.A. 43, 7442g, and 44, 1431e, in which it was shown that many arylbis(2haloalkyl) amines inhibited the growth of various animal tumors and of spontaneous and transmitted leukemia in the Furth AK 1 pure line; 2-C10H7N(CH2CH2Cl)2 has been used clinically for the treatment of various lymphadenopathies in human patients with encouraging results. 1,7-AcCl0H6NH2 (16 g.), added to 11.2 g. NaOH and 18.4 g. 50% N2H4.H2O in 175 g. (HOC2H4)20 and heated 3 hrs. at 195°, gives 14.5 g. 1,7-EtC10H6NH2, brown oil (Ac derivative, m. 167°). 1,2,3,4-Tetrahydronaphthalene (264 g.), nitrated according to Schroeter (C.A. 16, 1673), gives 60 g. 5-NO2 and 45 g. 6-NO2 derivs.; catalytic reduction (Raney Ni) gives 5,6,7,8-tetrahydro-1- and -2-naphthylamines. 1-Keto-1,2,3,4-tetrahydronaphthalene oxime, reduced with Na in EtOH, gives 1,2,3,4-tetrahydro-1-naphthylamine, b10 114°. These amines were

converted into the N,N-bis(2-hydroxyethyl) derivs. in the usual manner but it is preferable to use SOC12 in CHC13 for the chlorination stage,

N, N-Bis (2-chloroethyl) -2-methyl-1-naphthylamine, oil.

1,2,3,4-Tetrahydro-N,N-bis(2-hydroxyethyl)-1-naphthylamine, m. 89° (picrate, m. 140°); N, N-bis-(2-chloroethyl)-1,2,3,4-tetrahydro-1-

naphthylamine-HCl, m. 158°. 5,6,7,8-Tetrahydro-N,N-bis(2-

hydroxyethyl)-1-naphthylamine picrate, m. 199° (decomposition);

N, N-bis(2-chloroethyl)-5,6,7,8-tetrahydro-1-naphthylamine, an oil (picrate, m. 121°). N-(2-Naphthyl)-N-methyl-2-hydroxyethylamine

picrate, m. 160°; N-(2-naphthyl)-N-methyl-2-chloroethylamine, m.

52.5° (inactive); N-(2-naphthyl)-N-methyl-2-hydroxypropylamine picrate, m. 154°; N-(2-naphthyl)-N-methyl-2-chloropropylamine, m.

64° (inactive). N, N-bis(2-hydroxyethyl)-6-methyl-2-naphthylamine,

```
m. 94°; N,N-bis(2-chloroethyl)-6-methyl-2-naphthylamine, m.
65°; bis(2-bromoethyl) analog, m. 88°; bis(2-iodoethyl)
analog, m. 100-1°. N, N-Bis(2-chloroethyl)-8-methyl-2-
naphthylamine, m. 63°; 8-Et homolog, m. 48°;
bis(2-bromoethyl)-8-ethyl analog, m. 57°; bis(2-iodoethyl) analog,
m. 85°. 8-Acetyl-N, N-bis(2-hydroxyethyl)-2-naphthylamine, yellow,
m. 113°; bis(2-chloroethyl) analog, yellow, m. 84°;
bis(2-bromoethyl) analog, yellow, m. 94.5° (solns. of the last 2
compds. exhibit an intense yellow-green fluorescence).
N-(2-Chloroethyl)-1,2,3,4-tetrahydro-2-naphthylamine-HCl, m. 215°;
picrate, m. 197°. N,N-Bis(2-chloroethyl)-1,2,3,4-tetrahydro-2-naphthylamine-HCl, m. 164°; bis(2-bromoethyl) analog-HBr, m.
229°. 5,6,7,8-Tetrahydro-N,N-bis(2-hydroxyethyl)-2-naphthylamine,
m. 57°; bis(2-chloroethyl) analog, m. 65°, photoluminescent.
N, N-Bis (2-hydroxyethyl) -2-phenanthrylamine, m. 155°;
bis-(2-chloroethyl) analog, m. 91-2°; bis(2-bromoethyl) analog, m.
111-12°; bis(2-iodoethyl) analog, m. 117°.
N, N-Bis(2-hydroxyethyl)-3-phenanthrylamine, m. 109-10°;
bis(2-chloroethyl) analog, m. 73°; bis(2-bromoethyl) analog, m.
98°; bis(2-iodoethyl) analog, m. 125°. 2-(2-
Hydroxyethylamino)fluorene, yellow, m. 150° (cf. C.A. 43, 7442g);
2-chloroethyl analog, m. 127°. 2-[Bis(2-bromoethyl)amino]fluorene
m. 137°. N'-Propionyl-N, N-bis(2-chloroethyl)-p-phenylenediamine m.
101-3°. p-[Bis(2-chloropropyl)amino]benzoic acid, m. 165-6°;
Me ester, m. 61°. p-MeOC6H4N(CH2CH2Cl)2 (2.5 g.) and 3.4 g.
Et2NCS2Na in 200 ml. 50% aqueous Me2CO, refluxed 2 hrs., give
N,N-bis[2-(diethyldithiocarbamyl)ethyl]-p-anisidine, m. 85-6°.
p-MeOC6H4[NCH2CH(OH)CH2Cl]2 (40 g.) in 500 ml. boiling ether, gradually
treated with 40 g. KOH, gives N, N-bis(2, 3-epoxypropyl)-p-anisidine,
yellow, b9 228-9°; this is inactive. Data are given for the rate
of hydrolysis of a number of these compds. in 50% aqueous Me2CO at 66°.
The effect of various substituents is discussed. There is the expected
increase in the rate of hydrolysis on passing from the Cl to Br compound but
a somewhat surprising decrease for the iodides.
5379-46-4, Benzoic acid, p-[bis(2-chloropropyl)amino]-
   (preparation of)
5379-46-4 CAPLUS
Benzoic acid, 4-[bis(2-chloropropyl)amino]- (9CI) (CA INDEX NAME)
```